EP04/13416

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1. Your Reference	DMK/PB60598P	
2. Patent application number *(The Patent office will fill in this part)*	0327740.7	28 NOV 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB 473587003	
Patents ADP number *(if you know it)*		
If the applicant is a corporate body, give the country/state of its corporation	GB	
4 Title of the invention	NOVEL COMPOUNDS	
5 Name of your agent *(if you know one)*	DENISE MCKINNELL	
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY (CN9 25.1) 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS	
Patents ADP number *(if you know it)*	807255500 6	

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6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
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11. **I/We request the grant of a patent on the basis of this application**

Signature DMcKinnell **DENISE MCKINNELL** **28 November 2003**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

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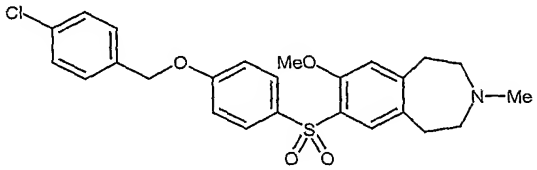
NOVEL COMPOUNDS

The present invention relates to novel salts of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a solvate thereof, pharmaceutical formulations, processes for their preparation, and their use in medicine.

The structure of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine is indicated below as the compound of formula (I):



(I)

The compound of formula (I) can be prepared by the reaction of 7-(4-fluorobenzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine with 4-chlorobenzyl alcohol in a suitable solvent, for example, tetrahydrofuran, in the presence of a base, for example, potassium *tert*-butoxide.

The hydrochloride salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine can be prepared by recrystallising 7-[4-(4-chlorobenzyloxy)benzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine free base from ethanol (following the addition of ethereal hydrogen chloride).

The compound of formula (I) and its hydrochloride salt have been found to be useful as an antipsychotic agent for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), mania, acute mania, paranoid and delusional disorders.

For use in medicine there exists a need for the compound to be prepared in a form suitable for ease of isolation in large scale manufacture and ease of formulating into an acceptable product for administration to patients. It is difficult to predict the physical characteristics of any particular salt of a compound and small, but significant, differences in physical properties may equate to large savings in the manufacture and formulation of a pharmaceutical product containing the compound.

The compound of formula (I) as a free base exists in multiple forms, some of which are hygroscopic. This affects the ease of handling of the free base under ambient conditions. The hygroscopicity affects the ability to accurately weigh the material, therefore control of atmospheric conditions, for example by use of a glove-box, are necessary to prevent the compound of formula (I) from absorbing water during procedures such as weighing out and formulation. It will be appreciated that it is vitally important to ensure consistent and accurate weight of active compound in a pharmaceutical composition.

The compound of formula (I) as the hydrochloride salt also exists in multiple forms and is also hygroscopic.

The present invention provides a novel salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine selected from maleate and p-toluenesulfonate, which may be used as an alternative to the free base and the hydrochloride salt of the compound of formula (I) for therapeutic administration or as an intermediate in the preparation of other salts. The invention also provides novel methods of preparation of these novel salts of the compound of formula (I) which are suitable for commercial use.

The maleate and tosylate salts of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine may be prepared by an efficient, economic and reproducible process particularly suited to large scale preparation.

The maleate and p-toluenesulfonate salts of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (hereinafter also referred to as "the maleate" and "the tosylate" respectively) have improved stability over the free base compound of formula (I) (hereinafter also referred to as "the free base") and its hydrochloride salt, particularly with respect to hygroscopicity.

These salts of the compound of formula (I) may be easier to manufacture than the free base and the hydrochloride salt and may be advantageous in the preparation of certain pharmaceutical compositions. The maleate and the tosylate are also easier to purify and provide higher purity products than the hydrochloride salt. There is also increased control over the final product form.

Therefore, as a first aspect of the present invention there is provided 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate.

In another aspect of the present invention there is provided 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate.

In a preferred aspect, 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate are substantially free of alternative salt, free base or impurity.

By "substantially free" is meant containing less than 10%, preferably less than 5%, more preferably less than 2%, of impurity. The impurity may be other compounds or other salts or solvates of the compound of formula (I).

In one aspect of the present invention there is provided 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate in which the ratio of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine to maleic acid (by mole) is 1:1.

In another aspect of the present invention there is provided 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate in which the ratio of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine to p-toluenesulfonic acid (by mole) is 1:1.

Depending on the solvent from which the maleate or the tosylate are recovered, the maleate or tosylate may be obtained as a solvate, such a solvate also forms one aspect of the present invention. The solvate is preferably a pharmaceutically acceptable solvate. A suitable solvate is a hydrate.

Alternatively, the maleate or tosylate may be obtained as anhydrates. The anhydrate contains less than 2% water, more preferably less than 1% water. The maleate or tosylate anhydrates demonstrate particular stability with respect to hygroscopicity and loss of water at ambient conditions. Furthermore, the maleate or tosylate anhydrates demonstrate reversible changes when exposed to very high humidity.

The present invention further includes a substantially non-hydrated and non-hygroscopic maleate salt or tosylate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine.

The present invention encompasses the maleate or a solvate thereof or the tosylate or a solvate thereof isolated in pure form or when admixed with other materials.

Therefore, in one aspect there is provided the maleate or a solvate thereof or the tosylate or a solvate thereof in isolated form.

In another aspect there is provided the maleate or a solvate thereof or the tosylate or a solvate thereof in pure form. Preferably the maleate or the tosylate are greater than 90% pure, more preferably greater than 95% pure, most preferably greater than 98% pure.

In a further aspect there is provided the maleate or a solvate thereof or the tosylate or a solvate thereof in non-crystalline form.

In a yet further aspect there is provided the maleate or a solvate thereof or the tosylate or a solvate thereof in crystalline form.

In a still further aspect there is provided the maleate or a solvate thereof or the tosylate or a solvate thereof in polymorphic form(s).

We have discovered that crystalline 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate and tosylate in which the ratio of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine to maleic acid and p-toluenesulfonic acid respectively (by mole) is 1:1 exists in at least one polymorphic form.

Accordingly a further aspect of the invention provides 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium(1:1) maleate having a melting point of 170 - 172°C and having a Raman or XRPD spectrum substantially as disclosed in Example 1 below.

Accordingly a further aspect of the invention provides 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium(1:1) tosylate having a melting point of 190 - 192°C and having a Raman or XRPD spectrum substantially as disclosed in Example 2 below.

The present invention also provides for the maleate or a solvate thereof or the tosylate or a solvate thereof when admixed with other material, for example another form of the compound of formula (I).

The maleate and the tosylate may be prepared by contacting appropriate stoichiometric amounts of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine free base with maleic acid and p-toluenesulfonic acid respectively. Preferably the base is in solution, more preferably both are in solution.

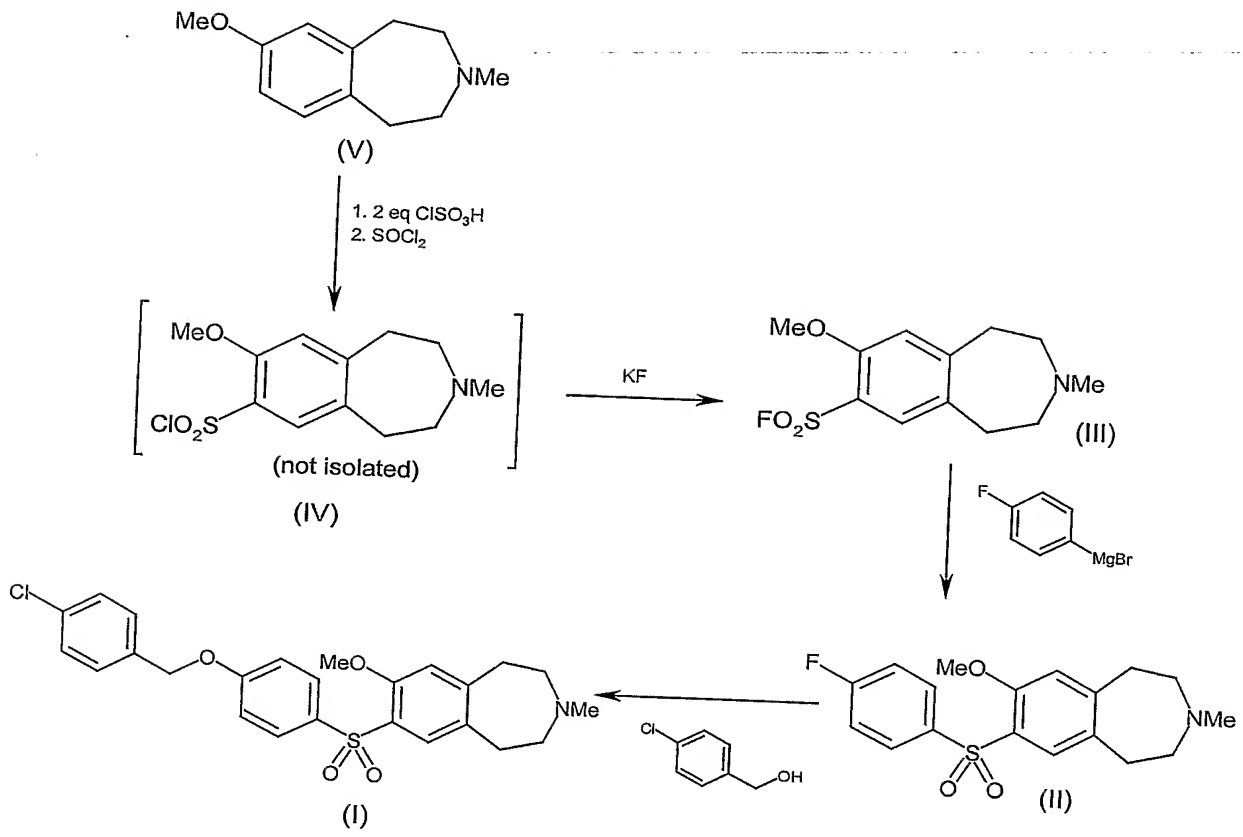
Most commonly used solvents are suitable for mobilising 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine free base, for example alcohols such as ethanol, ketones such as acetone, halogenated hydrocarbons such as dichloromethane, and ethers such as tetrahydrofuran. The maleic acid and the p-toluenesulfonic acid may each be added as a solid, but they are preferably added as a solution in an organic solvent such as ethanol, or water, methanol, propan-2-ol, or acetone.

For the preparation of the maleate or the tosylate salt, the concentration of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine base is preferably in the range 3 to 25% weight/volume, more preferably in the range 5 to 15%. The concentration of maleic acid or p-toulenesulfonic acid when used in solution is preferably in the range 0.5 to 5, more preferably in the range 1 to 2 molar. Elevated temperatures may be used to increase solubility.

The salts may be isolated in solid form by conventional means from a solution thereof obtained as above. For example, a non-crystalline salt may be prepared by precipitation from solution, spray drying and freeze drying of solutions, evaporating a solution to a glass, or vacuum drying of oils, or solidification of melts obtained from reaction of the free base and the acid.

Crystalline salts may be prepared by directly crystallising from a solvent in which the product has limited solubility, or by triturating or otherwise crystallising a non-crystalline salt. For example, 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate may be recrystallised from a variety of organic solvents, such as acetonitrile, butanone, *sec*-butanol, dichloromethane, ethanol, 3-pentanone, propan-2-ol and toluene. An improved yield of the salts is obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the production process and the particle size distribution and form of the product. Individual polymorphs are preferably crystallized directly from a solution of the salt, although recrystallizing a solution of one polymorph using seeds of another polymorph may also be carried out.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine [compound of formula (I)] may be prepared by Process (A) as set forth in Scheme 1 and in the examples.



Scheme 1

The compound of formula (I) may be prepared via the reaction of 4-chlorobenzyl alcohol with a base for example sodium hydride or potassium *tert*-butoxide and compound of formula (II), preferably in a suitable solvent, for example dimethyl sulfoxide or tetrahydrofuran.

A compound of formula (II) may be prepared by reacting a compound of formula (III), with 4-fluorophenylmagnesium bromide, in a suitable solvent, for example tetrahydrofuran, and optionally crystallising the product from diethyl ether or isopropyl acetate.

A compound of formula (III) may be prepared by reacting a compound of formula (IV), with a fluorinating agent, for example potassium fluoride.

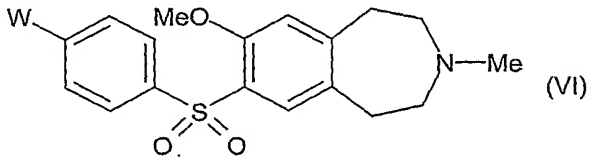
A compound of formula (IV) may be prepared by reacting a compound of formula (V), with a sulfonating agent, for example chlorosulfonic acid and thionyl chloride in a suitable solvent, for example acetonitrile.

A compound of formula (V) may be prepared using methods as described in the literature, for example using the route as described in European Patent EP285287.

4-Chlorobenzyl alcohol and 4-fluorophenylmagnesium bromide may be prepared according to known methods or are commercially available.

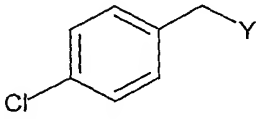
The compound of formula (I) may also be prepared by process (B), which process comprises:

reacting a compound of formula (VI)



(VI)

with a compound of formula (VII)



(VII)

wherein W is OH, and Y is a leaving group, such as bromo, iodo, chloro, fluoro, hydroxy, mesylate or triflate;
or Y is OH and W is a leaving group, such as fluoro, chloro, bromo or triflate.

Examples of general process (B) include:

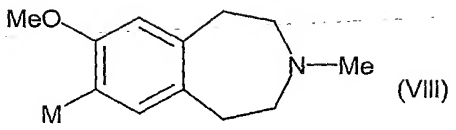
a) W is OH and Y is Br
which can be conveniently performed by heating the two reactants in an inert solvent e.g. dimethylformamide or dimethylsulfoxide, under basic conditions e.g. potassium carbonate or sodium hydride, optionally at elevated temperature e.g. 100°C.

b) W is OH and Y is OH
which can be conveniently carried out using Mitsunobu conditions in the presence of triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran at room temperature.

c) W is F and Y is OH
which can be conveniently carried out under basic conditions e.g. in the presence of sodium hydride in dimethylsulfoxide, optionally at elevated temperature.

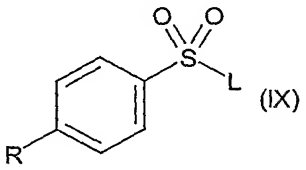
The compound of formula (I) may also be prepared by process (C) which process comprises:

reacting a compound of formula (VIII)



(VIII)

with a compound of formula (IX)

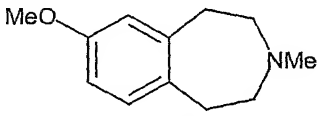


(IX)

wherein R is 4-chlorobenzyloxy, L is a leaving group, such as fluoro or chloro, and M is a metal, such as lithium or magnesium, or M is hydrogen. This general method (C) can be conveniently performed by mixing the two components at preferably -70°C to room temperature in a suitable solvent such as tetrahydrofuran or ether for 10 minutes to 18 hours. Alternatively, where M is H, this general method can be conveniently performed by treating (VIII) and (IX) with a Lewis acid under Friedel-Crafts conditions at elevated temperature in a suitable solvent.

In a further aspect of the invention there is provided a novel process for the preparation of a compound of formula (II) which process comprises:

reacting a compound of formula (V)



(V)

with 4-fluorobenzenesulfonyl chloride in the presence of a Lewis acid, for example, indium(III) triflate, tin(II) triflate, bismuth(III) chloride, or indium(III) chloride, and trifluoromethanesulfonic acid in a suitable solvent, for example, trifluoroacetic acid and, optionally, a co-solvent, for example dichloromethane.

In a further aspect of the invention there is provided a novel process for the preparation of the maleate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine comprising reacting 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine with maleic acid in a suitable solvent, for example, ethanol.

The maleate salt may be obtained as a solvate, when during isolation from solution it becomes associated with the solvent in which it is dissolved. Any such solvate forms a further aspect of this invention. Solvates may be returned to the unsolvated maleate salt

by heating, for example by oven-drying, or by treatment with a displacement solvent which does not form a solvate.

Prior to the isolation of the 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate, water may be removed from the solution containing the salt by azeotropic distillation to avoid the formation of hydrates or to obtain the product in anhydrous form. In that case, suitable solvents for the solution of the salt are those which form an azeotrope with water such as toluene and propan-2-ol. It should also be appreciated that mixtures of solvents can also be used to aid the azeotropic removal of water.

Maleic acid is commercially available.

In a still further aspect of the invention there is provided a novel process for the preparation of the tosylate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine comprising reacting a compound of formula (I) with p-toluenesulfonic acid in a suitable solvent, for example, acetone.

The tosylate salt may be obtained as a solvate, when during isolation from solution it becomes associated with the solvent in which it is dissolved. Any such solvate forms a further aspect of this invention. Solvates may be returned to the unsolvated tosylate salt by heating, for example by oven-drying, or by treatment with a displacement solvent which does not form a solvate.

Prior to the isolation of the 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate, water may be removed from the solution containing the salt by azeotropic distillation to avoid the formation of hydrates or to obtain the product in anhydrous form. In that case, suitable solvents for the solution of the salt are those which form an azeotrope with water such as toluene and propan-2-ol. It should also be appreciated that mixtures of solvents can also be used to aid the azeotropic removal of water.

p-Toluenesulfonic acid is commercially available.

Description of Figures:

Figure I shows X-Ray powder diffraction data obtained for the maleate as described in Example 1.

The maleate as described in Example 1 is characterised by having an XRPD pattern with signals substantially as listed in Table 1.

Figure 2 shows the Raman spectrum of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate.

Figure 3 shows a Differential Scanning Calorimetry (DSC) thermogram of 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate.

Figure 4 shows X-Ray powder diffraction data obtained for the tosylate maleate as described in Example 2.

The tosylate maleate as described in Example 2 is characterised by having an XRPD pattern with signals substantially as listed in Table 2.

Figure 5 shows the Raman spectrum of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate.

Figure 6 shows a DSC thermogram of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate.

It will be recognised that spectra and diffraction data will vary slightly according to various factors such as the temperature, concentration and instrumentation used. The skilled person will recognise that XRPD peak positions are affected by differences in sample height. The peak positions quoted herein are thus subject to a variation of +/- 0.15 degrees 2-theta.

The present invention also provides the anhydrous maleate salt of 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine characterised in that it provides an XRPD spectrum substantially as illustrated in Figure I.

The present invention further provides the anhydrous maleate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine characterised in that it provides an XRPD spectrum with signals substantially as listed in Table 1.

The present invention also provides the anhydrous tosylate salt of 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine characterised in that it provides an XRPD spectrum substantially as illustrated in Figure I.

The present invention further provides the anhydrous tosylate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-

benzazepine characterised in that it provides an XRPD spectrum with signals substantially as listed in Table 2.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate and tosylate salts have been found to exhibit affinity for dopamine receptors, in particular the D_3 and D_2 receptors, and are useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. These salts have also been found to have greater affinity for dopamine D_3 than for D_2 receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D_2 receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the dopamine D_3 receptor may give rise to beneficial antipsychotic activity without significant eps (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993).

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate and tosylate salts have also been found to have antagonist affinity for the serotonin 5-HT_{2C}, 5-HT_{2A} and 5-HT_6 receptors. These properties may give rise to anti-psychotic activity (e.g. improved effects on cognitive dysfunction) activity with reduced eps, and/or anxiolytic/antidepressant activity. These could include, but are not limited to, attenuation of cognitive symptoms via 5-HT_6 receptor blockade (see Reavill, C. and Rogers, D.C., 2001, Investigational Drugs 2, 104-109), and reduced anxiety (see for example Kennett et al., Neuropharmacology 1997 Apr-May; 36 (4-5): 609-20), protection against eps (Reavill et al., Brit. J. Pharmacol., 1999; 126: 572-574) and antidepressant activity (Bristow et al., Neuropharmacology 39:2000; 1222-1236) via 5-HT_{2C} receptor blockade.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate and tosylate salts may also exhibit affinity for other receptors not mentioned above, resulting in beneficial antipyschotic activity.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate and tosylate salts are of use as antipsychotic agent for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders. Furthermore, it may have utility as adjunct therapy in Parkinsons Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (e.g. see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242). From the localisation of D_3 receptors, it could also be envisaged that the maleate or tosylate could also have utility for the treatment of substance abuse where it has been suggested that D_3 receptors are involved (e.g. see Levant, 1997, Pharmacol. Rev., 49, 231-252). Examples of such substance abuse are

cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine and phencyclidine-like compounds, opiates such as cannabis, heroin, morphine, sedative ipnotic, amphetamine or amphetamine-related drugs such as dextroamphetamine or methylamphetamine abuse or a combination thereof. Other conditions which may be treated by the maleate or tosylate include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); anxiety disorders (which includes generalised anxiety and social anxiety disorder); agitation; tension; social or emotional withdrawal in psychotic patients; cognitive impairment including memory disorders (including Alzheimer's disease, dementia, amnesic disorders and age-associated memory impairment); psychotic states associated with neurodegenerative disorders, e.g. Alzheimer's disease; eating disorders (including anorexia nervosa and bulimia nervosa); obesity; sexual dysfunction; sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy); emesis; movement disorders; obsessive-compulsive disorders; amnesia; aggression; autism; vertigo; dementia; circadian rhythm disorders; convulsions; epilepsy; and gastric motility disorders e.g. IBS.

Therefore, the invention provides a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate as hereinbefore described or a pharmaceutically acceptable solvate thereof for use in therapy, in particular in the treatment of psychotic disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders.

The invention also provides a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate or a pharmaceutically acceptable solvate thereof for use in the treatment of a condition which requires modulation of a dopamine receptor.

The invention also provides a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate as hereinbefore described or a pharmaceutically acceptable solvate thereof for use in the treatment of psychotic disorders, schizophrenia, Parkinsons disease, substance abuse, dyskinetic disorders, depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general

medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); anxiety disorders (which includes generalised anxiety and social anxiety disorder); bipolar disorder, cognitive impairment including memory disorders (including Alzheimer's disease, dementia, amnesic disorders and age-associated memory impairment), eating disorders (including anorexia nervosa and bulimia nervosa), obesity, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy); emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

The invention also provides the use of a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate as hereinbefore described or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

The invention also provides the use of a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate as hereinbefore described or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for the treatment of psychotic disorders, schizophrenia, Parkinsons disease, substance abuse, dyskinetic disorders, depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); anxiety disorders (which includes generalised anxiety and social anxiety disorder); bipolar disorder, cognitive impairment including memory disorders (including Alzheimer's disease, dementia, amnesic disorders and age-associated memory impairment); eating disorders (including anorexia nervosa and bulimia nervosa); obesity, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy); emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders.

The invention also provides a method of treating a condition which requires modulation of a dopamine receptor, which comprises administering to a mammal in need thereof an effective amount of a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate as hereinbefore described or a pharmaceutically acceptable solvate thereof.

The invention also provides a method of treating psychotic disorders, schizophrenia, Parkinsons disease, substance abuse, dyskinetic disorders, depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive

episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); anxiety disorders (which includes generalised anxiety and social anxiety disorder); bipolar disorder, cognitive impairment including memory disorders (including Alzheimer's disease, dementia, amnesic disorders and age-associated memory impairment); eating disorders (including anorexia nervosa and bulimia nervosa); obesity, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy); emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders which comprises administering to a mammal in need thereof an effective amount of a salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium selected from maleate or tosylate as hereinbefore described or a pharmaceutically acceptable solvate thereof.

A preferred use for dopamine antagonists according to the present invention is in the treatment of psychotic disorders, schizophrenia, Parkinsons disease, substance abuse, dyskinetic disorders, depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion); anxiety disorders (which includes generalised anxiety and social anxiety disorder); bipolar disorder and cognitive impairment including memory disorders (including Alzheimer's disease, dementia, amnesic disorders and age-associated memory impairment).

"Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

It will be appreciated by those skilled in the art that 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as $5HT_3$ antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H_3 antagonists, $5HT_{1A}$ antagonists, $5HT_{1B}$ antagonists, $5HT_{1D}$ antagonists, D_1 agonists, M_1 agonists and/or anticonvulsant agents.

Suitable $5HT_3$ antagonists which may be used in combination of the compounds of the invention include for example ondansetron, granisetron and metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine and metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine and sertraline and zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

Suitable anticonvulsant agents which may be used in combination of the compounds of the inventions include for example divalproex, carbamazepine and diazepam.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

For use in medicine, 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate as hereinbefore described and a pharmaceutically acceptable carrier. The pharmaceutical composition can be for use in the treatment of any of the conditions described herein.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate may be administered by any convenient method, for example by oral, parenteral (e.g. intravenous), buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate as hereinbefore described can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-

benzazepinium maleate or tosylate in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochloro-hydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

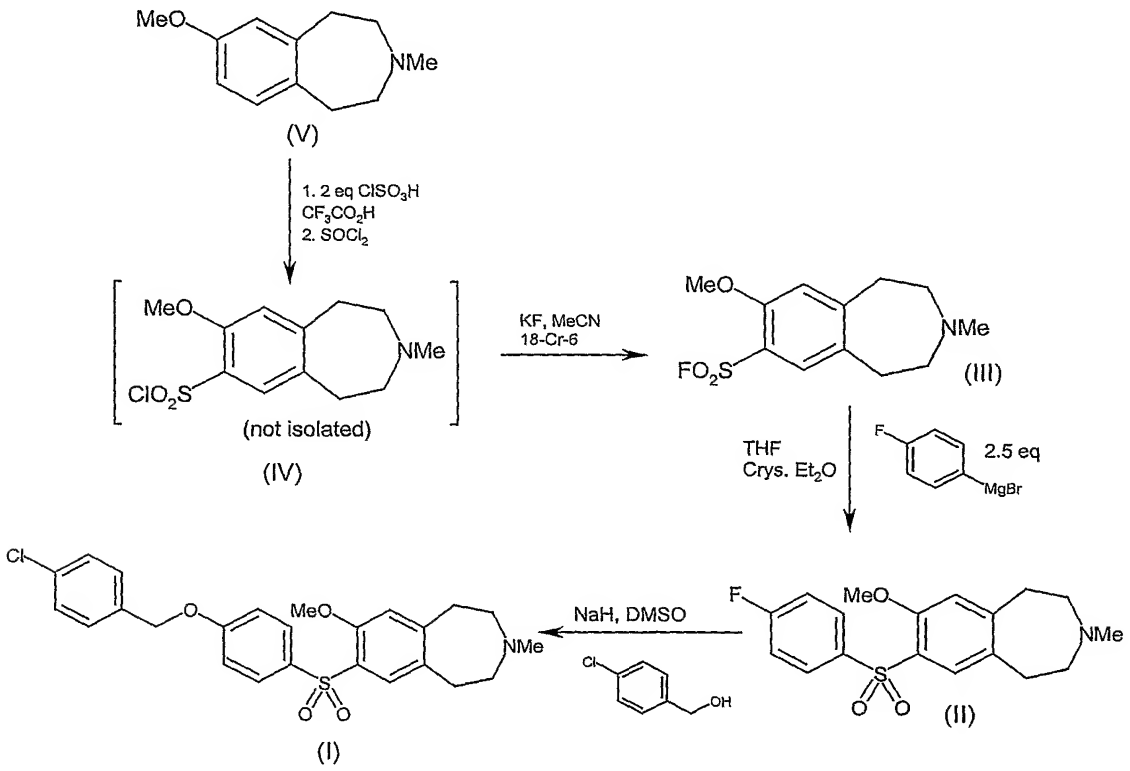
Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate thereof calculated as the free base.

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate or tosylate will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

No toxicological effects are indicated/expected when a compound of the invention is administered in the above mentioned dosage range.

The invention is further illustrated by the following non-limiting Scheme 2 and examples:

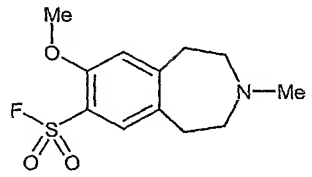
Preparation of 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine



Scheme 2

Description 1

8-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-sulfonyl fluoride (D1)



a) 8-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-sulfonic acid

7-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (see EP 285287) (23 g) was dissolved in trifluoroacetic acid (125 mL), and then stirred in an ice bath while chlorosulfonic acid (16.5 mL, 250 mmol) was added dropwise. The solution was stirred for 30 min, then evaporated to dryness to afford the title sulfonic acid which was used directly in the next step.

b) 8-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-sulfonyl chloride

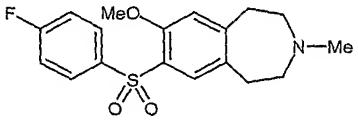
The sulfonic acid from part (a) was dissolved in thionyl chloride (75 mL) and the solution refluxed for 30 minutes. After cooling, the solution was evaporated to dryness to afford the title sulfonyl chloride which was used directly in the next step.

c) 8-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-sulfonyl fluoride

The sulfonyl chloride from part (b) was dissolved in acetonitrile (500 mL) and potassium fluoride (37 g, 625 mmol) and 18-crown-6 (1 crystal) added. The mixture was stirred for 18 h, then quenched with cold aqueous sodium bicarbonate solution until pH equalled 8. The mixture was extracted twice with ethyl acetate, washed with bicarbonate solution then brine, dried and evaporated to afford the sulfonyl fluoride D1 (25 g).

Description 2a

7-(4-Fluoro-benzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D2)



8-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-sulfonyl fluoride (25 g) was dissolved in dry tetrahydrofuran (250 mL) and 4-fluorophenylmagnesium bromide in tetrahydrofuran (2.5 equivalents) added over 15 min with ice bath cooling, an exotherm only apparent during the first part of the addition. The resulting mixture was stirred overnight without cooling then added over 10 min to a solution of sodium potassium tartrate tetrahydrate (250 g) in water (450 mL) with stirring. Diethyl ether was added (400 mL) and the organic layer separated, dried, evaporated, and crystallised from diethyl ether to give crystalline fluorophenyl sulfone D2 17 g (51%).

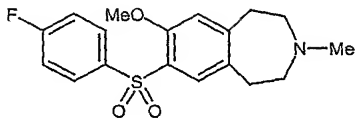
Description 2b

7-(4-Fluorobenzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D2)

(i) 7-Methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium trifluoroacetate

Trifluoroacetic acid (2 mL) was added to a solution of 7-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5 g) in isopropyl acetate (20 mL), maintaining the temperature below 30°C. n-Heptane (20 mL) was added at 25°C, the mixture seeded and stirred at 20 - 25°C to crystallize the product. The resulting solid was filtered, washed with n-heptane (10 mL) and dried under vacuum at 40 – 45°C to give the title product as an off-white solid (6.4 g). Mp 91 - 92°C; δ_H (400 MHz, DMSO) 2.84 (3H, s, NC$\underline{H}_3$), 2.90 - 3.57 (8H, br m, C$\underline{H}_2$C$\underline{H}_2$), 3.73 (3H, s, OC$\underline{H}_3$), 6.76 (1H, d, J = 8 Hz, ArH), 6.83 (1H, s, ArH), 7.13 (1H, d, J = 8 Hz, ArH), 10.26 (1H, br s, NH^+); MS (ES+) *m/z* 192 (MH^+).

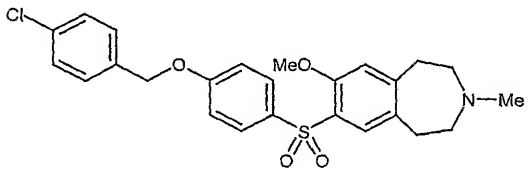
(ii) 7-(4-Fluorobenzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine



Trifluoromethanesulfonic acid (2.2 mL, 25 mmol) was added to a mixture of 7-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium trifluoroacetate (5 g, 16.4 mmol), 4-fluorobenzenesulfonyl chloride (4.8 g, 25 mmol), and indium(III) chloride (0.36 g, 1.6 mmol) in trifluoroacetic acid (10 mL) at ambient temperature, under a nitrogen atmosphere. The resulting mixture was heated under reflux for 7 hours then cooled and diluted with dichloromethane (25 mL) followed by water (15 mL) maintaining the temperature below 20°C. When the addition was complete, the pH was adjusted to 2 by the addition of 40% w/v aqueous sodium hydroxide (15 mL) and the phases separated. Water (10 mL) was added, followed by 10% w/v aqueous sodium hydroxide to adjust the pH to 10. The phases were separated and the organic phase washed with water (15 mL), dried ($MgSO_4$) and filtered. The filtrate was diluted with isopropyl acetate (35 mL) and concentrated under reduced pressure to a residual volume of 15 mL and stirred at ambient temperature to crystallise the product. The resulting slurry was stirred in an ice bath for 1 hour, filtered, the cake washed with 2:1 heptane:isopropyl acetate (10 mL) and dried at 40°C under vacuum to give the title product as a white solid (4.06 g). Mp 129 - 130°C; δ_H (400 MHz, DMSO) 2.23 (3H, s, NC$\underline{H}_3$), 2.44 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 2.87 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 3.70 (3H, s, OC$\underline{H}_3$), 6.97 (1H, s, ArH), 7.40 (2H, dd, J = 9.0, 9.0 Hz, ArH), 7.70 (1H, s, ArH), 7.94 (2H, dd, J = 9.0, 5.2 Hz, ArH); MS (ES+) *m/z* 391 [70%, (MH^+ +CH_3CN)], 350 (100%, MH^+).

Description 3

Preparation of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D3)

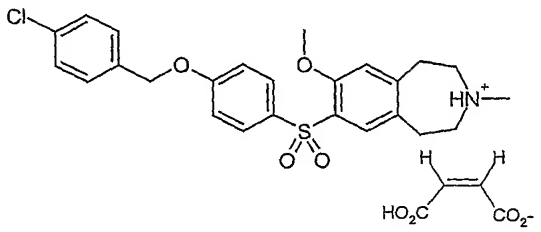


A solution of 4-chlorobenzyl alcohol (4.9 g, 34.4 mmol) in tetrahydrofuran (20 mL) was added drop-wise to a solution of potassium *tert*-butoxide (4.9 g, 43.2 mmol) in tetrahydrofuran (30 mL) maintaining the temperature below 25°C. The resulting mixture was stirred under nitrogen for 10 minutes then a solution of 7-(4-fluorobenzenesulfonyl)-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10 g, 28.6 mmol) in tetrahydrofuran (45 mL) was added drop-wise maintaining the temperature below 25°C and the mixture stirred for 1.75 hours. 10% w/v Aqueous ammonium chloride (50 mL) was added and the mixture stirred for 5 minutes. The phases were separated, water (70 mL) was added to the organic phase and the mixture stirred at 15 - 25°C for 1.5 hours. The resulting solid was filtered, the cake washed with water (20 mL) and dried at 50°C under

vacuum to yield the title product as a white solid (10.99 g). Mp 120 - 122°C; δ_H (400 MHz, DMSO) 2.25 (3H, s, $NC\underline{H}_3$), 2.46 (4H, m, $C\underline{H}_2C\underline{H}_2$), 2.88 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.70 (3H, s, $OC\underline{H}_3$), 5.19 (2H, s, $ArC\underline{H}_2$), 6.95 (1H, s, ArH), 7.16 (2H, dd, J = 7.0, 2.0 Hz, ArH), 7.46 (4H, m, ArH), 7.68 (1H, s, ArH), 7.81 (2H, dd, J = 7.0, 2.0 Hz, ArH); MS (ES+) *m/z* 513 [100%, $(MH^+ + CH_3CN)$], 472 (60%, MH^+), 192 (45%).

Example 1

Preparation of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate



A solution of maleic acid (27.1 g, 233.4 mmol) in ethanol (100 mL) was added portionwise to a boiling solution of 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (100.1 g, 212.0 mmol) in ethanol (1.05 L) and the resulting solution allowed to stir for 10 minutes and return to reflux. The solution was cooled to 75°C, seeded with maleate salt (100.8 mg) then cooled to ambient temperature. The resulting slurry was stirred at ambient temperature for 2 hours and filtered; the cake was washed with ethanol (300 mL) and dried under vacuum at 60°C to yield the title product as a white solid (122.4 g). Mp 170 - 172°C; δ_H (400 MHz, DMSO) 2.81 (3H, s, $NC\underline{H}_3$), 3.10 (4H, br s, $C\underline{H}_2C\underline{H}_2$), 3.34 (4H, br s, $C\underline{H}_2C\underline{H}_2$), 3.72 (3H, s, $OC\underline{H}_3$), 5.18 (2H, s, $ArC\underline{H}_2$), 6.02 (2H, s, -C<u>H</u>=C<u>H</u>-), 7.07 (1H, s, ArH), 7.17 (2H, dd, J = 7, 2.04, ArH), 7.46 (4H, m, ArH), 7.80 (2H, dd, J = 7, 2.04, ArH), 7.82 (1H, s, ArH), 9.0 – 10.0 (1H, br s, NH^+); MS (ES+) *m/z* 513 [100%, $(MH^+ + CH_3CN)$], 472 (80%, MH^+), 192 (45%).

Table 1: XRPD angles and d spacings for 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate

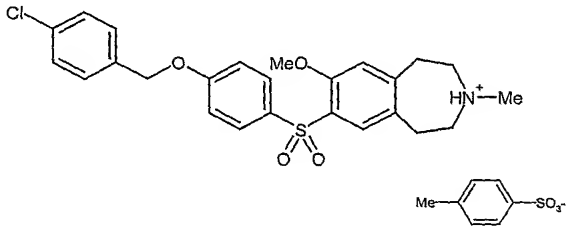
Pos.[°2Th.]	d-spacing[Å]
5.9	15.0
9.6	9.2
11.3	7.8
11.5	7.7
14.8	6.0
16.2	5.5
16.9	5.2
17.2	5.1
18.8	4.7

Pos.[°2Th.]	d-spacing[Å]
22.0	4.0
24.6	3.6
25.9	3.4
26.9	3.3
30.4	2.9

Data obtained for the maleate are shown in Figures 1 – 3 and Table 1.

Example 2

7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium toluenesulfonate



A solution of *para*-toluenesulfonic acid (105 mg, 0.55 mmol) in acetone (1 mL) was added dropwise to a solution of 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (255 mg, 0.54 mmol) in acetone (1.5 mL) at 50°C. The resulting solution was stirred at 50°C for 30 minutes then cooled to ambient temperature and stirred for 1 hour. The resulting slurry was filtered, the filter cake washed with acetone (2.5 mL) and dried under vacuum at 45°C to yield the title compound as a white solid (329 mg). Mp 190 - 192°C;δ_H (400 MHz, DMSO) 2.35 (3H, s, ArC$\underline{H}_3$), 2.90 (3H, s, NC$\underline{H}_3$), 3.09-3.19 (6H, br m, C$\underline{H}_2$C$\underline{H}_2$), 3.65 (2H, br s, C$\underline{H}_2$C$\underline{H}_2$), 3.79 (3H, s, OC$\underline{H}_3$), 5.26 (2H, s, ArC$\underline{H}_2$), 7.14-7.18 (3H, m, ArH), 7.22-7.25 (2H, m, Ar$\underline{H}$), 7.50-7.55 (6H, m, Ar$\underline{H}$), 7.86-7.89 (3H, m, Ar$\underline{H}$), 9.73 (1H, br s, NH^+).

Table 2: XRPD angles and d spacings for 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate.

Pos.[°2Th.]	d-spacing[Å]
5.7	15.5
6.4	13.8
9.6	9.2
11.5	7.7
12.1	7.3
13.8	6.4

Pos.[°2Th.]	d-spacing[Å]
14.1	6.3
14.5	6.1
15.8	5.6
16.5	5.4
17.2	5.2
18.7	4.7
19.5	4.5
19.9	4.5
20.4	4.4
21.0	4.2
21.3	4.2
21.8	4.1
22.2	4.0
22.8	3.9
23.4	3.8
23.8	3.7
24.5	3.6
25.1	3.6
26.0	3.4
27.3	3.3
28.3	3.2
29.1	3.1
30.5	2.9
33.4	2.7
34.4	2.6

Data obtained for the tosylate are shown in Figures 4 – 6 and table 2.

X-Ray Powder Diffraction

X-Ray Powder Diffraction (XRPD) analysis was performed on a Phillips X'pert Pro powder diffractometer, using an X'Celerator detector. The acquisition conditions were; radiation: Cu K_α, generator tension: 40 kV, generator current: 45mA, start angle: 2.0 °2θ, end angle: 40.0 °2θ, step size: 0.0167 °2θ , time per step: 31.75 seconds. The sample was prepared using backfill technique.

Raman Spectroscopy

Raman spectra were recorded in an NMR tube using a Nicolet 960 E.S.P. FT-Raman spectrometer, at 4 cm^{-1} resolution with excitation from a Nd:VO_4 laser (1064 nm) with a power output of 400mW. An absolute threshold of 0.5 and sensitivity of 65% were applied for the purpose of peak selection.

Differential Scanning Calorimetry (DSC)
DSC thermograms were recorded using a Perkin Elmer Diamond DSC. The sample was heated at 10 °C min^{-1} in an open pan.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein. They may take the form of product, process or use claims and may include, by way of example and without limitation, the claims that follow.

CLAIMS

1. A salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine selected from maleate and tosylate or a solvate thereof.

2. A salt as claimed in claim 1 wherein the salt is maleate.

3. A salt as claimed in claim 1 wherein the salt is tosylate.

4. A salt according to any of claims 1 to 3 wherein the ratio of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine to maleic acid or p-toluenesulfonic acid (by mole) is 1:1.

5. A salt according to any of claims 1 to 4 in crystalline form.

6. A pharmaceutical composition comprising a salt as claimed in any of claims 1 to 5 and a pharmaceutically acceptable carrier.

7. A salt according to any of claims 1 to 5 for use in therapy.

8. A salt according to any of claims 1 to 5 for use in the treatment of a psychotic disorder.

9. A salt according to claim 8 wherein the psychotic disorder is schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders.

10. Use of a salt according to any of claims 1 to 5 in the manufacture of a medicament for the treatment of a psychotic disorder.

11. Use of a compound of formula (I) according to claim 10 wherein the psychotic disorder is schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders.

12. A method of treatment of a psychotic disorder in mammals including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) according to any of claims 1 to 5.

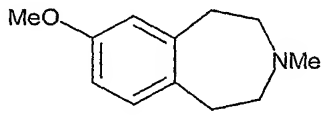
13. A method of treating a psychotic disorder according to claim 12 wherein the disorder is schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression, mania, acute mania, paranoid and delusional disorders.

14. A maleate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine substantially as disclosed in Example 1.

15. A tosylate salt of 7-[4-(4-chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine substantially as disclosed in Example 2.

16. A process for the preparation of a salt according to any of claims 1,2 ,4 or 5 by crystallisation or recrystallisation from a solution of a 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate.

17. A process for the preparation of a compound of formula (II) comprising reacting a compound of formula (V)



(V)

with 4-fluorobenzenesulfonyl chloride in the presence of a Lewis acid.

18. A process for the preparation of a salt as claimed in any of claims 1, 2, 4 or 5 comprising reacting 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine with maleic acid.

19. A process for the preparation of a salt as claimed in any of claims 1, 3, 4 or 5 comprising reacting 7-[4-(4-chlorobenzyloxy)-benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine with p-toluenesulfonic acid.

Figure I XRPD for 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate, characteristic XRPD angles and d spacings are recorded in Table 1.

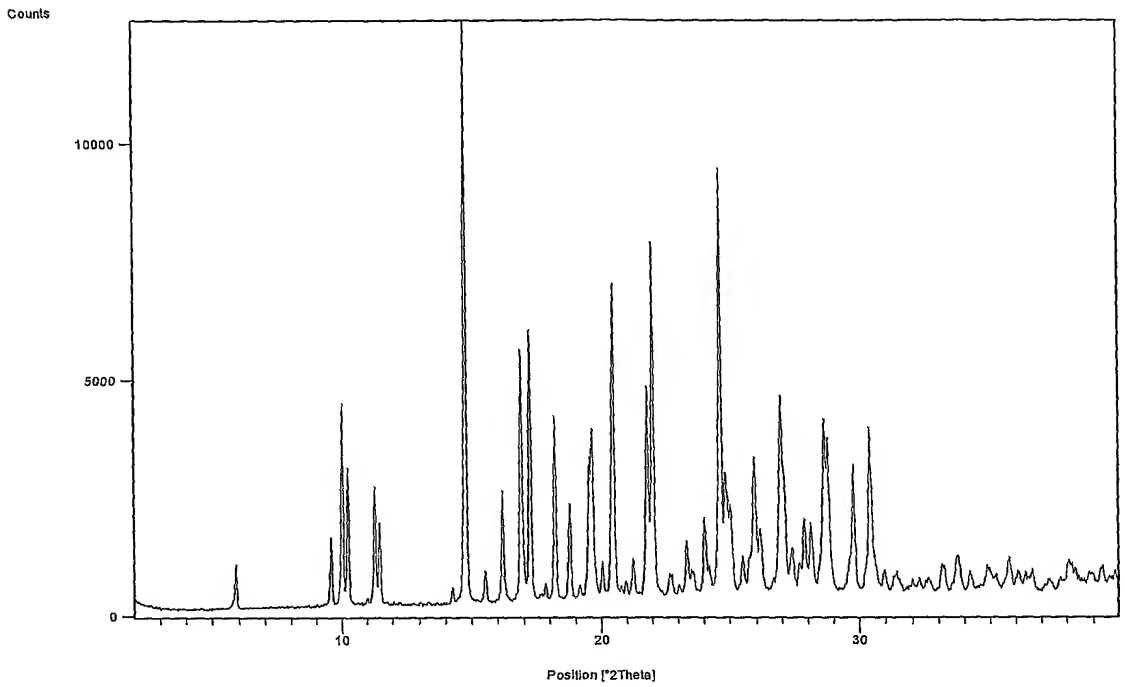
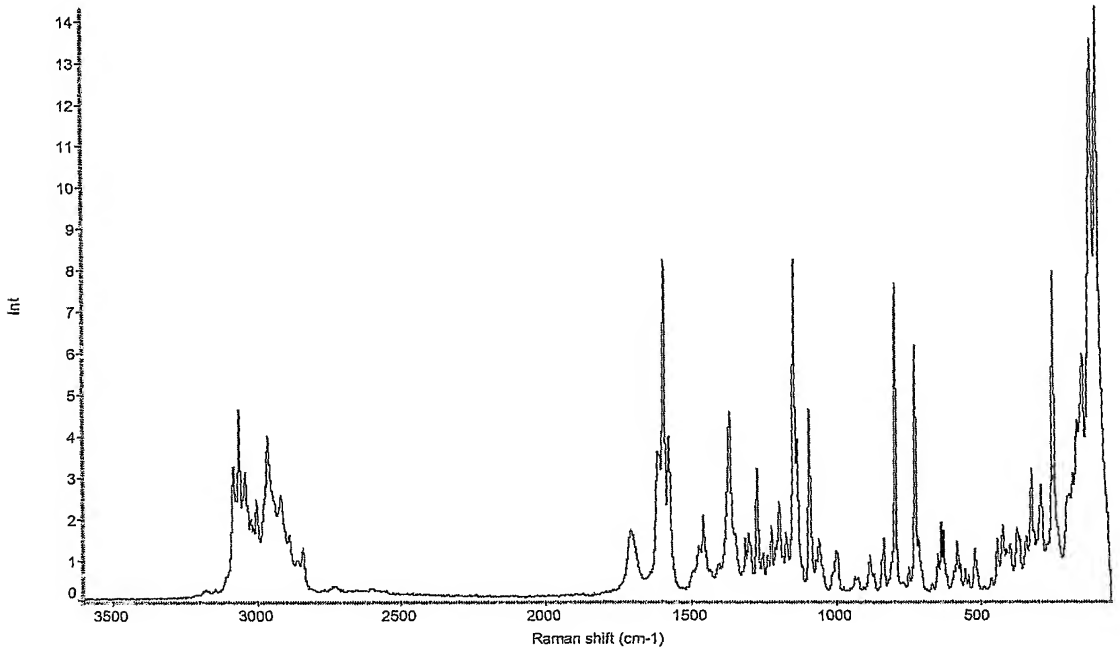


Figure 2: Raman spectrum of 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate



Bands were observed at: 3082, 3062, 3042, 3002, 2963, 2918, 2843, 1702, 1611, 1590, 1574, 1459, 1369, 1316, 1305, 1276, 1256, 1239, 1226, 1199, 1176, 1148, 1136, 1093, 1060, 1000, 924, 883, 836, 795, 750, 727, 648, 636, 628, 582, 555, 520, 441, 421, 396, 372, 341, 322, 289, 247, 178, 162, 144, 113, 93 cm^{-1}.

Figure 3: DSC thermogram of 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium maleate

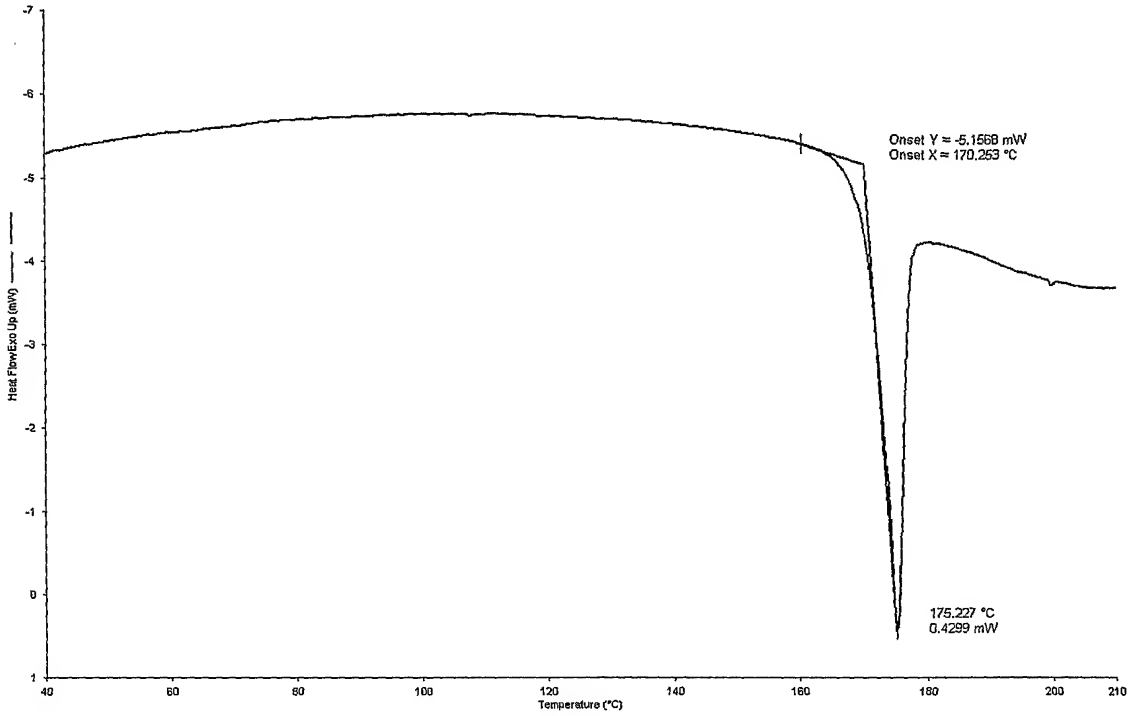


Figure 4 XRPD for 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate, characteristic XRPD angles and d spacings are recorded in Table 2.

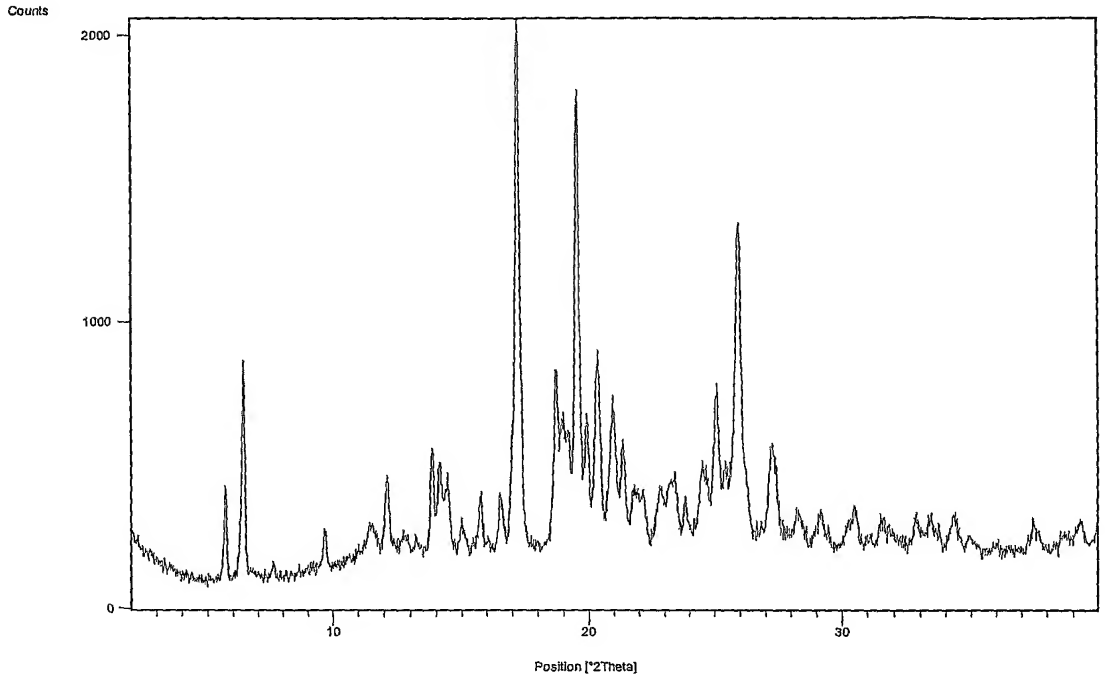
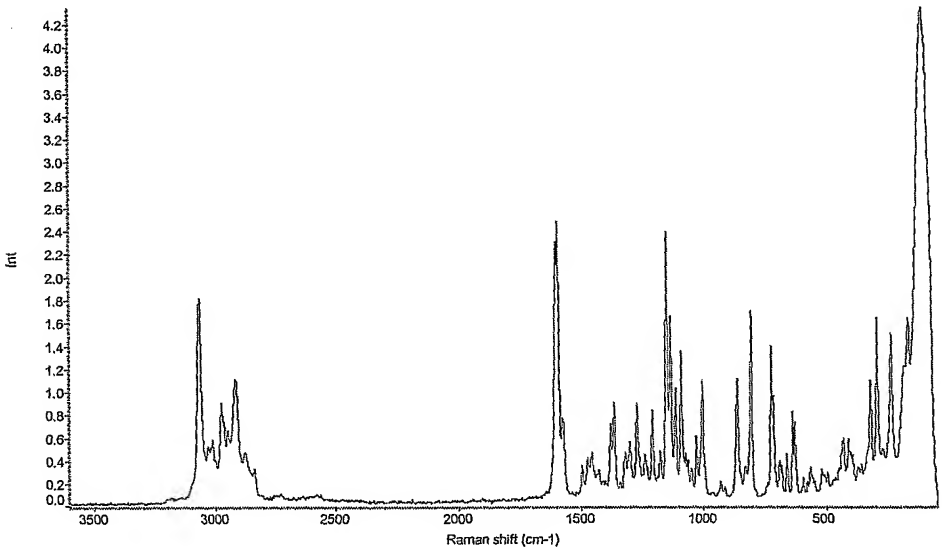


Figure 5: Raman spectrum of 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate.



Bands were observed at: 3068, 3012, 2975, 2947, 2915, 2877, 1600, 1592, 1575, 1495, 1457, 1379, 1365, 1319, 1301, 1272, 1240, 1210, 1178, 1151, 1135, 1113, 1090, 1049, 1027, 1003, 927, 859, 801, 721, 689, 659, 637, 627, 593, 564, 518, 495, 430, 408, 320, 293, 236, 168, 109 cm^{-1}.

Figure 6: DSC thermogram of 7-[4-(4-Chlorobenzyloxy)benzenesulfonyl]-8-methoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepinium tosylate